

950.872



PATENT SPECIFICATION

NO DRAWINGS

950.872

Inventors: JACQUES BOISSIER, ROGER RATOUIS

Date of filing Complete Specification: March 16, 1962.

Application Date: March 17, 1961.

No. 9856/61.

Complete Specification Published: Feb. 26, 1964.

© Crown Copyright 1964.

Index at acceptance:—C2 C(1G5A, 1G5B, 1G6B1, 1G6B4, 3A13C1C, 3A13C2C, 3A13C3C, 3A13C10F, 3A13C10H, B4A1, B4A2, B4M)

International Classification:—C 07 d

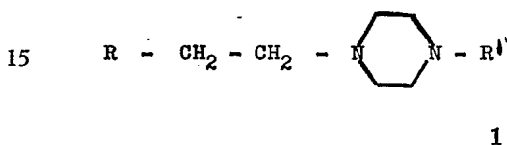
COMPLETE SPECIFICATION

Substituted Pyridyl-Ethyl-Piperazines

We, SOCIÉTÉ INDUSTRIELLE POUR LA FABRICATION DES ANTIBIOTIQUES (S.I.F.A.) of 67, Boulevard Haussmann, Paris 8e, France, a body corporate organised under the laws of France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new piperazine derivatives and a process for the preparation thereof.

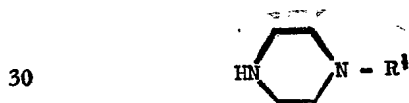
The present invention provides novel compounds of the general formula:



in which R represents a 2 - pyridyl or 4 - pyridyl radical, and R¹ represents a 2 - pyridyl radical, a phenyl radical, a 2-halogenophenyl radical, a 2 - alkoxyphenyl radical containing up to 10 carbon atoms or a 2 - alkylphenyl radical containing up to 10 carbon atoms.

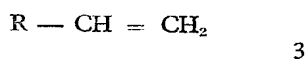
The invention also provides salts of the compounds of the above general formula 1 with mineral or organic acids, and the invention also provides a process for the preparation of these salts.

The novel compounds can be prepared by reacting an N - monosubstituted piperazine of the general formula:



[Price 4s. 6d.]

with a vinyl pyridine of the general formula:



in which formula R¹ and R have the meaning indicated above. The reaction takes place on heating in the presence of a polymerisation inhibitor for vinyl pyridines. The desired product can be isolated by conventional methods on completion of the reaction.

It is preferred to work at a temperature between 140° C. and 160° C. in the presence of hydroquinone or tert. butyl catechol and using the N - monosubstituted piperazine in a slight excess. It is also desirable to operate without a solvent.

Thus a mixture containing a vinyl pyridine, a 10% excess of an N - monosubstituted piperazine and 1 part of tert. butyl catechol per 1000 parts of vinyl pyridine can be heated for 2 hours to 150° C. The desired compound can be isolated by recrystallisation from a suitable solvent, after driving off unreacted starting materials by distillation under reduced pressure.

The salts of the novel compounds can be prepared by reacting a compound of formula (1) above with a mineral or organic acid.

The compounds of the present invention have very interesting pharmacodynamic properties. They are depressants of the central nervous system and are hypotensors. They also have antihistaminic properties. For this reason, they can be used therapeutically in the treatment of anxiety and hypertension conditions and they can also be used as antihistamines. They are usually administered orally.

In therapeutic use, these new compounds are either used in the form of a base, or in the form of pharmaceutically acceptable addition salts, such as the salts obtained with sulphuric, hydrochloric, hydrobromic, phosphoric, acetic,

maleic, citric, tartaric, salicylic, benzoic and cinnamic acids.

The active therapeutic doses can be varied according to the subjects, the seriousness of the cases, the method of administration and the effect which is desired. Generally speaking, the useful (i.e. effective non - toxic) dosology with a human being is between 20 mg. and 1 g. per day.

The present invention also provides therapeutic compositions, which are suitable for oral, rectal, or parenteral administration, comprising an inert pharmaceutically acceptable carrier or diluent and one or more of the derivatives of formula (1), used in the form of a base or salt. Examples of suitable carriers or diluents are starch, calcium carbonate, alginic acid, lactose, magnesium stearate, cocoa butter, aqueous or non-aqueous liquid vehicles, vegetable oils, and various wetting, dispersing and emulsifying agents. The compositions intended for parenteral use are sterilised by using the conventional sterilisation methods.

The following non - limiting Examples further illustrate the present invention:

EXAMPLE 1

A mixture of 10.5 g. of rectified 2 - vinyl pyridine, 18 g. of N - phenyl piperazine and 10 mg. of tert. butyl catechol is brought to 150°C. by heating, in a flask equipped with a reflux condenser, on an oil bath for two hours.

After cooling the starting products which have not reacted are distilled under a reduced pressure of 0.05 to 0.2 mm. Hg., the temperature of the heating bath being 180 to 200°C.

The residue from this distillation is solidified by cooling.

It is recrystallised from 400 cc. of petroleum ether (fraction boiling between 60 and 75°C.) and there are obtained 14 g., (i.e. a yield of 53%) of N - β - (2 - pyridyl) - ethyl - N¹-phenyl piperazine which melts as 58°C., on a heating stage microscope.

Analysis: $C_{17}H_{21}N_3$

	C	H
Calculated %	76.36	7.92
Found %	76.5	8.0

This product has a DL 50 of 100 mg/kg. when applied intraperitoneally to a mouse. When injected intravenously into a dog, it reverses the action of adrenalin and produces a distinct hypotension with a dose of 0.5 mg/kg.

EXAMPLE 2

Using the process described in Example 1 and starting from 10.5 g. of rectified 4 - vinyl pyridine and 18 g. of N - phenyl piperazine, there are obtained 10.3 g., (i.e. a yield of 39%) of N - β - (4 - pyridyl) - ethyl - N¹-phenyl piperazine on recrystallisation from

petroleum ether (fraction boiling between 50 and 60°C.). This compound melts at 83°C., on a heating stage microscope.

Analysis: $C_{17}H_{21}N_3$

	C	H
Calculated %	76.36	7.92
Found %	76.6	8.0

This product as a DL 50 of 100 mg/kg. when administered intraperitoneally to a mouse. When injected intravenously into a dog, it reverses the effects of adrenalin and causes a marked hypotension from a dose of 0.250 mg/kg.

EXAMPLE 3

Using the process described in Example 1 and starting from 10.5 g. of 2 - vinyl pyridine and 18 g. of N - (2 - pyridyl) piperazine, there are obtained 12 g., (i.e. a yield of 45%), of N - β - (2 - pyridyl) - ethyl - N¹ - (2-pyridyl) piperazine, on recrystallisation from heptane. This compound melts at 69°C., on a heating stage microscope.

Analysis: $C_{18}H_{20}N_4$

	C	H
Calculated %	71.61	7.51
Found %	71.6	7.5

This product has a DL 50 of 110 mg/kg. when administered intraperitoneally to a mouse. When injected intravenously into a dog, it causes a strong and lasting hypotension at a dose of 0.5 mg/kg.

EXAMPLE 4

Using the process described in Example 1 and starting from 10.5 g. of 4 - vinyl pyridine and 18 g. of N - (2 - pyridyl) piperazine, there are obtained 10 g., (i.e. a yield of 37%) of N - β - (4 - pyridyl) - ethyl - N¹ - (2-pyridyl) piperazine on recrystallisation from 60% aqueous ethanol. This compound melts at 82°C., on a heating stage microscope.

Analysis: $C_{18}H_{22}N_4$

	C	H
Calculated %	71.61	7.51
Found %	71.9	7.3

This product has a DL 50 of 220 mg/kg. when administered intraperitoneally to a mouse. When injected intravenously into a dog, it causes a marked hypotension from the dose of 0.2 mg/kg.

EXAMPLE 5

Using the process described in Example 1 and starting from 10.5 g. of 2 - vinyl pyridine and 21.6 g. of N - (2 - chlorophenyl) piperazine, there are obtained 15 g., (i.e. a yield of 50%) of N - β - (2 - pyridyl) - ethyl - N¹ - (2 - chlorophenyl) piperazine on recrystallisation from a mixture of petroleum ether (fraction boiling between 35 and 50°C.) and heptane. This compound melts at 64°C. on a heating stage microscope.

Analysis: $C_{17}H_{20}ClN_3$

	C	H
Calculated %	67.65	6.68
Found %	67.7	6.65

- 5 This product has a DL 50 of 100 mg/kg. when administered intraperitoneally to a mouse, when injected intravenously into a dog, it causes a hypotension and reverses the effects of adrenalin from doses of 0.2 and 0.5 mg/kg.

EXAMPLE 6

- 10 Using the process described in Example 1 and starting from 10.5 g. of 4 - vinyl pyridine and 21.6 g. of N - (2 - chlorophenyl) piperazine, there are obtained 18 g., (i.e. a yield of 60%) of N - β - (4 - pyridyl) - ethyl - N¹ - (2 - chlorophenyl) piperazine on recrystallisation from hexane. This compound melts at 69°C., on a heating stage microscope.

Analysis: $C_{17}H_{20}ClN_3$

- | | C | H |
|--------------|-------|------|
| Calculated % | 67.65 | 6.68 |
| Found % | 67.65 | 6.6 |

- 20 This product has a DL 50 of 150 mg/kg. when administered intraperitoneally to a mouse. When injected intravenously into a dog, it causes hypotension from the dose of 0.2 mg./kg. this being maintained for more than 2½ hours after injection. Furthermore, it suppresses the effects of adrenalin in a dose of 0.5 mg/kg. and suppresses the effects of noradrenalin in a dose of 5 mg/kg.; in a concentration of 1×10^{-7} , it inhibits 50% of the effects of adrenalin on the isolated seminal vesicles of a guinea pig. This same derivative is found to be a depressant of the central nervous system of the mouse in a dose of 20 mg/kg., administered intraperitoneally.

EXAMPLE 7

- 40 Using the process described in Example 1 and starting from 10.5 g. of 2 - vinyl pyridine and 21.1 g. of N - (2 - methoxyphenyl) piperazine, there are obtained 7 g., (i.e. a yield of 24%) of N - β - (2 - pyridyl) - ethyl - N¹ - (2 - methoxyphenyl) piperazine on recrystallisation from hexane. This compound melts at 47°C., on a heating stage microscope.

Analysis: $C_{18}H_{23}N_3O$

- | | C | H |
|--------------|-------|------|
| Calculated % | 72.69 | 7.79 |
| Found % | 72.0 | 7.4 |

- 50 This product has a DL 50 of 60 mg/kg. when administered intraperitoneally to a mouse, when injected intravenously into a dog, in doses of 0.2 mg/kg. and 0.5 mg/kg., it causes a strong hypotension and a reversal of the adrenalin effects.

EXAMPLE 8

- 60 Using the process described in Example 1 and starting from 10.5 g. of 4 - vinyl pyridine and 21.1 g. of N - (2 - methoxyphenyl) piperazine, there are obtained 14 g., (i.e. a

yield of 48%) of N - β - (4 - pyridyl)ethyl - N¹ - (2 - methoxyphenyl) piperazine on recrystallisation from heptane. This compound melts at 98°C., on a heating stage microscope. 65

Analysis: $C_{18}H_{23}N_3O$

	C	H
Calculated %	72.69	7.79
Found %	72.6	7.8

- 70 This product has a DL 50 of 150 mg/kg. when administered intraperitoneally to a mouse. When injected intravenously into a dog, it causes the reversal of the adrenalin effects from the dose of 0.2 mg/kg. The dose of 0.5 mg/kg. causes a stable hypotension for almost 3 hours and the dose of 1 mg/kg. suppresses the effects of noradrenalin. The same substance inhibits 50% of the effects of adrenalin on the isolated seminal vesicles of a guinea pig in a concentration of 1×10^{-7} . This derivative has proved to be a depressant of the central nervous system in a dose of 20 mg/kg. when administered intraperitoneally to a mouse. 75 80

EXAMPLE 9

- 85 In accordance with the process described in Example 1, and starting from 10.5 g. of 4 - vinyl - pyridine and 26.5 g. of N - (2 - bromophenyl) - piperazine, there are obtained 15.2 g. (i.e. a yield of 44%) of N - β - (4 - pyridyl) - ethyl - N¹ - (2 - bromophenyl) piperazine on recrystallisation from hexane, this melting at 73°C. on a heating stage microscope. 90

Analysis: $C_{17}H_{20}BrN_3$

	C	H
Calculated %	58.96	5.82
Found %	59.3	5.8

EXAMPLE 10

- 100 According to the process described in Example 1, and starting from 10.5 g. of 4 - vinyl - pyridine and 22.6 g. of N - (2 - ethoxyphenyl) - piperazine, there are obtained 10.3 g. (i.e. a yield of 33%) of N - β - (4 - pyridyl) - ethyl - N¹ - (2 - ethoxyphenyl) piperazine, on recrystallisation from heptane, this substance melting at 66°C. on a heating stage microscope. 105

Analysis: $C_{19}H_{25}N_3O$

	C	H
Calculated %	73.28	8.09
Found %	73.5	8.1

EXAMPLE 11

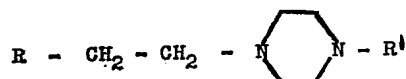
- 115 According to the process described in Example 1, and starting from 10.5 g. of 4 - vinyl - pyridine and 18.3 g. of N - (2 - methylphenyl) - piperazine, there are obtained 14 g. (i.e. a yield of 50%) of N - β - (4 - pyridyl) - ethyl - N¹ - (2 - methylphenyl) piperazine, which melts at 68°C. on a heating stage microscope. 120

Analysis: $C_{18}H_{23}N_3$

	C	H
Calculated %	76.83	8.24
Found %	76.7	8.3

5 WHAT WE CLAIM IS:—

1. Piperazine derivatives of the general formula



10 and acid addition salts thereof in which formula R represents a 2 - pyridyl or 4 - pyridyl radical and R^1 represents a 2 - pyridyl radical, a phenyl radical, a 2 - halogenophenyl radical, a 2 - alkoxyphenyl radical containing up to 10 carbon atoms of a 2 - alkylphenyl radical containing up to 10 carbon atoms.

15 2. N - β - (2 - pyridyl) - ethyl - N^1 - phenyl piperazine and acid addition salts thereof.

3. N - β - (4 - pyridyl) - ethyl - N^1 - phenyl piperazine and acid addition salts thereof.

20 4. N - β - (2 - pyridyl) - ethyl - N^1 - (2 - pyridyl) piperazine and acid addition salts thereof.

5. N - β - (4 - pyridyl) - ethyl - N^1 - (2 - pyridyl) piperazine and acid addition salts thereof.

25 6. N - β - (2 - pyridyl) - ethyl - N^1 - (2 - chlorophenyl) piperazine and acid addition salts thereof.

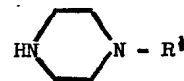
7. N - β - (4 - pyridyl) - ethyl - N^1 - (2 - chlorophenyl) piperazine and acid addition salts thereof.

30 8. N - β - (2 - pyridyl) - ethyl - N^1 - (2 - methoxyphenyl) piperazine and acid addition salts thereof.

35 9. N - β - (4 - pyridyl) - ethyl - N^1 - (2 - methoxyphenyl) piperazine and acid addition salts thereof.

10. A process for the preparation of com-

pounds as claimed in claim 1, which comprises reacting an N - substituted piperazine 40 of the general formula



with a vinyl pyridine of the general formula



(R and R^1 having the same meaning as in claim 1), the reaction being carried out by heating in the presence of a polymerisation inhibitor for vinyl pyridines. 45

11. A process as claimed in claim 10, wherein the reaction is performed at 140°C to 160°C in the presence of hydroquinone or tertiary butyl catechol, as polymerisation inhibitor. 50

12. A process for the preparation of compounds as claimed in claim 1, substantially as described with reference to any of Examples 1 to 8. 55

13. A process as claimed in any of claims 10 to 12, wherein the compound formed is subsequently treated with an acid to form the acid addition salt thereof. 60

14. A pharmaceutical composition which comprises an effective non - toxic amount of a compound as claimed in any of claims 1 to 9 and an inert pharmaceutically acceptable carrier or diluent. 65

ELKINGTON AND FIFE,
Chartered Patent Agents,
Bank Chambers, 329 High Holborn,
London, W.C.1.
Agents for the Applicants.